UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/258,217	02/26/99	KEATING M	2323-127

HM12/0202

STEPHEN A SAXE PHD
ROTHWELL FIGG ERNST AND KURZ
SUITE 701 EAST
555 13TH STREET N W
WASHINGTON DC 20004

EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	7

DATE MAILED: 02/02/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/258,217	Applicant(s) Zhou et al.
	Examiner Shin-Lin Chen	Group Art Unit 1633

☒ Responsive to communication(s) filed on *Dec 16, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-6, 9, and 10* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6, 9, and 10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election of group I (claims 1-6, 9 and 10) in Paper No. 6, filed 12-16-1999, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 7, 8 and 11-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 6.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 5 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using ELN +/- mice to study vascular disease, does not reasonably provide enablement for a method of using any ELN +/- organisms other than ELN +/- mice to screen drugs useful for treating humans with SVAS, hypertension or atherosclerosis . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 5 is directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using an ELN +/- organism, wherein said drug candidates inhibit occlusion of arteries. Claim 9 is directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using ELN +/- organisms or ELN +/- cells and by measuring the synthesis of elastin mRNA. Claims 5 and 9 encompass any ELN +/- organisms including humans, other mammals, fish, birds, insect, plants and microorganism.

The specification discloses the generation of ELN +/- mice. The specification fails to provide an enabling disclosure for the preparation of any and all ELN +/- organism except ELN +/- mice, because it fails to provide sufficient guidance for the preparation of any ELN +/- organism other than ELN +/- mice and further because it fails to provide a suitable description of the ELN +/- organisms used for the claimed method. No teachings are present within the specification in regard to how one would have prepared any ELN +/- organisms having a predictable phenotype as shown in applicant's ELN +/- mice other than ELN +/- mice without the skilled practitioner having to engage in undue experimentation to practice the invention over the full scope claimed.

The state of the art in the field of transgenics at the time of the invention was unpredictable. Transgene expression and phenotypic/physiological results of such expression is not always accurately predictable. For example, the incidence of expression of the same fusion gene is much higher in transgenic mice than in pigs, introduction of human growth hormone

transgene in mouse results in mammoth mouse phenotype whereas introduction of same transgene into pigs results in several health problems, including lameness, lethargy, gastric ulcers, and anoestrous gilts (Palmiter et al., 1983 (e.g. abstract, W); Pursel et al. 1990.(e.g. abstract, X)).

Similarly, the phenotype of a transgenic knockout organism is unpredictable. Different species of organism may differ dramatically immunologically, physiologically, and morphologically, and the approach to produce transgenic knockout organism may differ. For example, the opacity of the cytoplasm of pig ova makes visualization of pronuclei extremely difficult, therefore, centrifugation of pig ova at 10,000-15,000g for 3-5 minutes has been used before microinjecting DNA into pig pronuclei, whereas this step is not necessary for making transgenic mice (Pursel et al., 1990 (X), e.g. p. 236). Houdebine, 1994 (U2) points out that transgene expression in transgenic animal is heavily dependent on its site of integration in the host genome rather than on the number of copies, the site of integration of a gene is unpredictable and thus the expression of a transgene in a given animal is unpredictable when the DNA is microinjected into the pronuclei by the conventional method (e.g. p. 277). Houdebine also indicates that although ES cells can be used to generate transgenic animals, but this approach remains restricted to mice, ES cells from other species are not presently available (e.g. p. 279). Seamark, 1994 (V2) points out that even pig's pluripotent ES cells can be created, no group has demonstrated totipotency of these cells through reinstating their genome within a germ line, and procedures for reinstating the ES cell genome into a germ line are still far from routine.

Small changes in the environment the embryo is exposed to can impact on development with long-term implications on health and warefare. For example, in the mouse, brief exposure of preimplantation embryos to in vivo culture conditions can both result in substantial phenotypic variation and predicate the subsequent expression and penetration of some transgenes. Asynchrony between the stage of development of the embryo and tract at embryo transfer can also affect development (e.g. p. 654, 655). In view of the inherent unpredictability of the phenotype of transgenic animals in general, and the lack of availability of embryonic stem cells for species other than mouse indicate that the claimed animals or organisms and method of using said animals or organisms would have also been unpredictable and thus would require more description and guidance than taught in the specification as filed for one to have been able to practice that claimed invention.

The quantity of experimentation includes determining how to generate various types of ELN +/- organisms to overcome the potential problems because of their different physical structure and physiological characteristics, determining the phenotype of each ELN +/- organism, breeding various types of ELN +/- organism, determining whether elastin is associated with the phenotype and screening the drug useful for treating humans with SVAS, hypertension or atherosclerosis.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to have made and used the invention over the full scope claimed. This is particularly true given the nature of the invention, the state of the prior

art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 1 and 3 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Li et al., 1998 (AE).

Claim 1 is directed to a mouse comprising one functional elastin gene and either one nonfunctional or no second elastin gene in its genome. Claim 3 is directed to a mouse cell comprising one functional elastin gene and either one nonfunctional or no second elastin gene in its genome.

Li et al. generated mice hemizygous for the elastin gene (ELN +/-), wherein ELN mRNA and protein were reduced by 50%, but the number of elastic lamellae and smooth muscle in ELN +/- mice arteries increased 35% (e.g. abstract). The mice set forth above contain mouse cells which is hemizygous for the elastin gene (ELN +/-). Thus, claims 1 and 3 are clearly anticipated by Li et al..

7. Claims 2 and 4 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Li et al., 1998 (AC).

Claim 2 is directed to a mouse comprising a genome with no functional elastin gene. Claim 4 is directed to a mouse cell comprising a genome with no functional elastin gene.

Li et al. generated transgenic mouse comprising no functional elastin gene, ELN-/-, and showed absence of ELN mRNA and protein in ELN -/- mice. The ELN -/- mice survived gestation but dies by postnatal day 4.5. The mice set forth above contain mouse cells comprising a genome with no functional elastin gene. Thus, claims 2 and 4 are clearly anticipated by Li et al..

8. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sechler et al., 1994 (U).

Claim 1 is directed to a mouse comprising one functional elastin gene and either one nonfunctional or no second elastin gene in its genome. Claim 3 is directed to a mouse cell comprising one functional elastin gene and either one nonfunctional or no second elastin gene in its genome. Claim 2 is directed to a mouse comprising a genome with no functional elastin gene. Claim 4 is directed to a mouse cell comprising a genome with no functional elastin gene.

Sechler et al. disclosed construction of transgenic mice that contain rat tropoelastin gene (elastin gene) lacking exon sequences within the 5' or 3' end of the gene, e.g. lacking exon 33 or exons 19-31. The transgenic mice disclosed by Sechler et al. includes hemizygous ELN +/- and homozygous ELN -/-. Thus the claims are clearly anticipated by Sechler et al..

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 5, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reitamo et al., 1994 (V) in view of Li et al., 1998 (AE), Su et al., 1997 (N) and Li et al., 1997 (AD).

Claim 5 is directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using an ELN +/- organism, wherein said drug candidates inhibit occlusion of arteries. Claims 9 and 10 are directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using ELN +/- organisms or ELN +/- cells and by measuring the synthesis of elastin RNA and elastin, respectively.

Reitamo et al. teach generating transgenic mice expressing a human elastin promoter/CAT reporter gene construct and injecting IL-10 subcutaneously into said transgenic mice. Reitamo et al. also teach a method of screening a compound which can stimulate the elastin promoter *in vivo or in vitro,* and show IL-10 up-regulates elastin gene expression *in vivo* by CAT assay (transgenic mice skin) and *in vitro* by measuring the elastin mRNA level using Northern analysis (e.g. abstract, p. 332). Reitamo et al. do not teach using ELN +/- organisms or

ELN +/- cells to screen drug candidate useful for treating atherosclerosis hypertension or SVAS in a human by measuring the synthesis of elastin or screen drug which inhibits occlusion of arteries.

Li et al. (AE) teach generating mice hemizygous for the elastin gene (ELN +/-), wherein ELN mRNA and protein were reduced by 50%, but the number of elastic lamellae and smooth muscle in ELN +/- mice arteries increased 35% (e.g. abstract). The mice set forth above contain mouse cells which is hemizygous for the elastin gene (ELN +/-). Su et al. teach a diagnostic assays for detecting the levels of human cytokine polypeptide protein in cells and tissues by using radioimmunoassays, competitive-binding assays, western blot analysis or ELISA assays. In addition, Li et al. (AD) teach elastin point mutations cause an obstructive vascular disease, supravalvular aortic stenosis (SVAS), which is an inherited disease that affects the aorta, carotid, coronary and pulmonary arteries.

The mutation of elastin gene is associated with SVAS, an inherited obstructive vascular disease that affects the aorta, carotid, coronary and pulmonary arteries. Using ELN +/- mice or ELN +/- mouse cells one would have been able to screen for drugs or compounds useful for treating humans with SVAS, hypertension or atherosclerosis which are diseases associated with arteries. In view of the collective teachings of Reitamo et al., Li et al. (AD) and Su et al., one of ordinary skill in the art would have been motivated at the time of filing to use the ELN +/- mice or mouse cells taught by Li et al. (AE) to screen for drugs or compounds useful for treating SVAS, atherosclerosis or hypertension in a human by measuring the synthesis of elastin mRNA

or elastin, or the drug or compound which can inhibit the occlusion of arteries because ELN +/- mice have only about 50% of elastin mRNA and protein as compared to the ELN +/+ mice, a drug or compound that can increase the expression elastin mRNA or protein, or inhibit the occlusion of arteries, since the discovery of such compounds would have been useful for treating humans with SVAS, hypertension or atherosclerosis. Thus, it would have been prima facie obvious for a person of ordinary skill to have practiced the claimed invention with reasonable expectation of success because a method of screening drug using transgenic mice by measuring the synthesis of mRNA or protein were well known in the art as taught by Reitamo et al. and Su et al...

11. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maruyama et al., 1991 (W2) in view of Sechler et al., 1995 b(U).

Claim 6 is directed to a method to screen for drug candidates useful for treating humans with atherosclerosis, SVAS or hypertension by measuring activity of elastase in the presence of drugs wherein said drugs which inhibit elastase are said drug candidates.

Maruyama et al. teach in rats injected with the toxin monocrotaline and administered SC-39026, a serine elastase inhibitor, pulmonary hypertension was decreased in association with reduced muscularization of peripheral pulmonary arteries. SC-39026 reduced the number of muscularized arteries and the level of pulmonary arterial pressure during exposure to chronic hypoxia, and decreased the elastase activity. The effect of elastase inhibitor on the hypertension was determined by transmission electron microscopic analysis of pulmonary arteries and by assay

of elastolytic activity which determines elastase activity. A different elastase inhibitor, α1-proteinase inhibitor, showed an even greater reduction in hypoxia-induced pulmonary hypertension (e.g. abstract, p. H1719). Maruyama et al. do not correlate elastin with SVAS and atherosclerosis.

Sechler et al. teach that there are a variety of disorders characterized by abnormal elastin synthesis and a concomitant deposition of aberrant elastic fiber, such as hypertension, atherosclerosis, actinic elastosis, Marfan's syndrome and SVAS, and mutations in the tropoelastin gene (elastin gene) plays a role in analogous human disorders of elastic tissue, including SVAS (e.g. p. 149).

Sechler et al. teach that there was an association between aberrant deposition of elastin and human disorders such as hypertension, atherosclerosis and SVAS, and Maruyama et al. teach that effect of elastase inhibitor, such as SC-39026, on hypertension was determinable by measuring the elastase activity and the elastase inhibitor shows a reduction in hypoxia-induced pulmonary hypertension, and that elastase is the enzyme which degrades elastin (Maruyama et al., page. H1716). One of ordinary skill in the art would have been motivated to combine the teachings of Sechler et al. and Maruyama et al. to screen drug candidates useful in treating human disorders, such as hypertension, atherosclerosis and SVAS, by measuring the elastase activity in the presence of drugs wherein said drugs inhibit elastase, i.e. an elastase inhibitor, because elastase inhibitor that was known to inhibit elastase activity showed a reduction in hypoxia-induced pulmonary hypertension in rats and it might also have same effect in humans.

Thus, it would have been prima facie for a person of ordinary skill in the art to have practiced the claimed invention recited in claim 6 with reasonable expectation of success because measuring the elastase activity to identify a potential elastase inhibitor was known to have been routine and well known in the art.

Conclusion

No claims is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP 1800